10/070281 - 05 MAR 2002
JC05 Rec'd PCT/PTO

Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		P32411 U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) unknown 10/070281
INTERNATIONAL APPLICATION NO PCT/GB00/03366	INTERNATIONAL FILING DATE 01 September 2000	PRIORITY DATE CLAIMED 03 September 1999
TITLE OF INVENTION PROCESS FOR PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES		
APPLICANT(S) FOR DO/EO/US Sungwook CHO, Hoon CHOI, John David HAYLER		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [x] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [x] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/GB00/03366, filed September 1, 2000, which claims benefit from the following Priority Application: 9920917.3 GB, filed September 3, 1999.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

US APPLICATION NO (if known see 37 CFR 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEYS DOCKET NO.
10/070281	PCT/GB00/03366	P32411

20. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**	**890.00**	
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) **$710.00**		
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,040.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0.00**	

Claims	Number Filed	Number Extra	Rate		
Total claims	**21 - 20 =**	**1**	**1 x $18.00**	**$18.00**	
Independent claims	**2 - 3 =**	**0**	**0 x $84.00**	**$0.00**	
Multiple dependent claims (if applicable)			**+ $280.00**	**$0.00**	
			TOTAL OF ABOVE CALCULATIONS =	**$18.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
			SUBTOTAL =	**$908.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
			TOTAL NATIONAL FEE =	**$908.00**	
				Amount to be refunded	**$**
				charged	**$**

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$908.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-6897
Facsimile (610) 270-5090

SIGNATURE
Loretta J. Henderson
NAME
37,347
REGISTRATION NO.

n:\loretta\applications\p3's\p32411\nat'l.doc

PATENT
ATTORNEY'S DOCKET NUMBER P32411

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE (DO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/03366	01 September 2000	03 September 1999

TITLE OF INVENTION
PROCESS FOR PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES

APPLICANT(S) FOR DO/US
Sungwook CHO, Hoon CHOI, John David HAYLER

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231
ATTENTION: DO/US

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Transmittal Letter, Form PTO 1390 and the papers indicated as being transmitted therewith, and Post Card are being deposited with the United States Postal Service on this date March 1, 2002 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EV000522792US addressed to the:

Assistant Commissioner for Patents, Washington, D.C. 20231.

Elsa Matos
(Typed or printed name of person mailing paper)

Elsa Matos
(Signature of person mailing paper)

20462
PATENT TRADEMARK OFFICE

"EXPRESS MAIL CERTIFICATE"
"EXPRESS MAIL" MAILING LABEL NUMBER EV000522792US
DATE OF DEPOSIT 01 March 2002

Attorney Docket No. P32411

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/03366	01 September 2000	03 September 1999

TITLE OF INVENTION
PROCESS FOR PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES

APPLICANT(S) FOR DO/US
Sungwook CHO, Hoon Choi, John David HAYLER

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231
ATTENTION: DO/US

PRELIMINARY AMENDMENT

Sir:

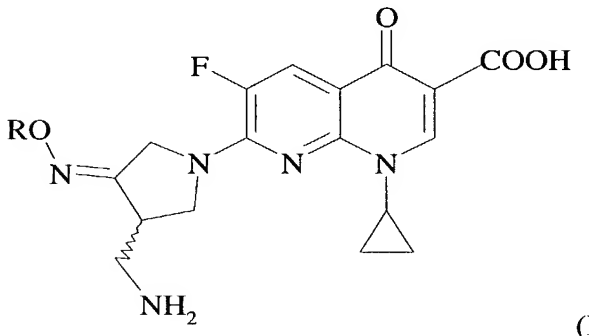
Prior to calculation of the filing fee and the first Office Action on the merits, the Applicants request entry of the following amendment.

IN THE SPECIFICATION:

Please insert the following Abstract of the Disclosure on a separate page:

ABSTRACT OF THE DISCLOSURE

A process for the production of Naphthyridine-3-carboxylic acid derivatives of formula (I) having antibacterial activity.

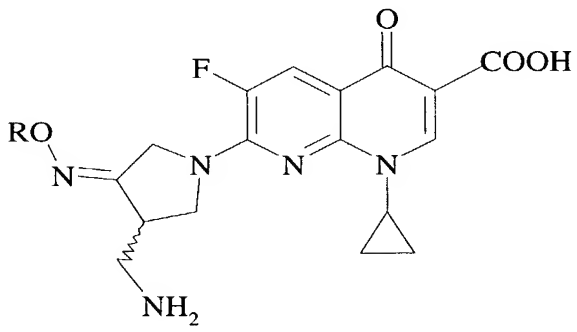


(I)

IN THE CLAIMS:

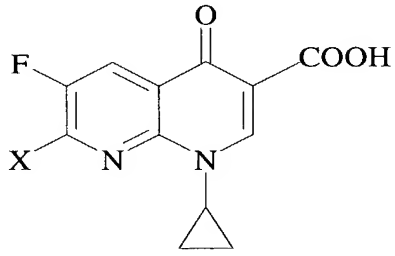
Please cancel claims 2-11 without prejudice to or disclaimer of their subject matter. Please amend claim 1 to read as follows, and add the following new claims 12-31.

1. (once amended) A process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:



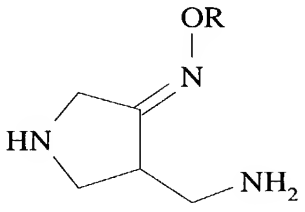
(I)

wherein R is C_{1-4} alkyl or C_{1-4} haloalkyl, which comprises reaction of a compound of formula (II):



(II)

wherein X is a leaving group; with a compound of formula (III):



(III)

wherein R is as defined for formula (I), or a salt thereof;

in the presence of a base and an aqueous solvent, wherein the solvent is water;

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

12. The process according to claim 1 wherein 10 volumes of solvent based on the compound of formula (II) are used.

13. The process according to claim 1 wherein between 1.01 and 1.08 mole equivalents of the compound of formula (III) based on the compound of formula (II) are used.

14. The process according to claim 1 performed at a temperature between ambient and about 60°C.

15. The process according to claim 1 wherein the base is triethylamine, diisopropylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,4-diazabicyclo[2.2.2]octane, or a tetraC_{1-6}alkylammonium hydroxide.

16. The process according to claim 1 wherein the base is triethylamine or a tetraC_{1-6}alkylammonium hydroxide.

17. The process according to claim 1 wherein the base is triethylamine.

18. The process according to claim 1 wherein between 3.2 and 3.8 mole equivalents of base is used based on the compound of formula (II), and wherein the compound of formula (III) is in the form of the dimethanesulfonate salt, the hydrochloride salt, the trifluoroacetate salt, or the sulfate salt.

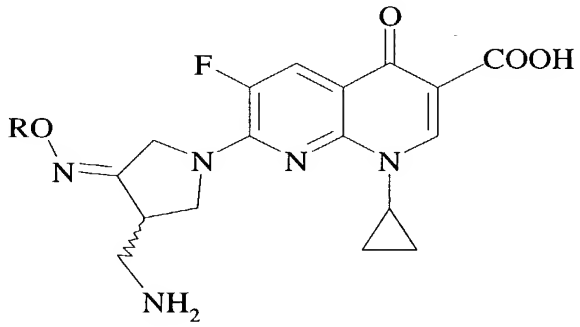
19. The process according to claim 1 wherein X is chloro.

20. The process according to claim 1 wherein the compound of formula (III) is 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

21. The process according to claim 1 wherein R is C_1 alkyl.

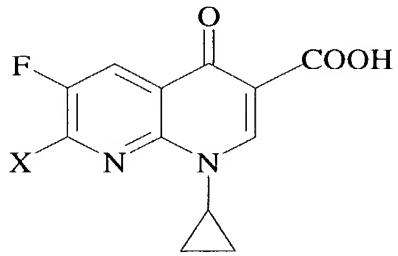
22. The process according to claim 1 wherein the compound of formula (I) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof.

23. A process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:



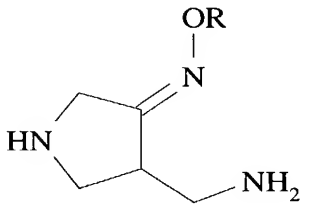
(I)

wherein R is C_{1-4} alkyl or C_{1-4} haloalkyl, which comprises reaction of a compound of formula (II):



(II)

wherein X is a leaving group; with a compound of formula (III):



(III)

wherein R is as defined for formula (I), or a salt thereof;

in the presence of a base and an aqueous solvent; wherein the base is triethylamine, diisopropylamine, or a tetraC_{1-6}alkylammonium hydroxide;

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

24. The process according to claim 23 wherein the base is triethylamine or a tetraC_{1-6}alkylammonium hydroxide.

25. The process according to claim 23 wherein the base is triethylamine.

26. The process according to claim 23 wherein the base is tetrabutylammonium hydroxide or tetramethylammonium hydroxide.

27. The process according to claim 23 wherein the solvent is aqueous acetonitrile, an aqueous alcohol or water.

28. The process according to claim 23 wherein when the solvent is aqueous acetonitrile a ratio of between 0.7 and 1.4 acetonitrile:water is used.

29. The process according to claim 23 wherein the compound of formula (III) is 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

30. The process according to claim 23 wherein R is C_1 alkyl.

31. The process according to claim 23 wherein the compound of formula (I) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof.

REMARKS

Upon entry of this amendment, claims 1 and 12-31 will be pending in the application. Claim 1 has been amended. A marked-up version of claim 1 as amended is attached hereto as Appendix 1.

Support for this preliminary amendment is found in the claims as originally filed, and in the specification at page 2, lines 19-21, page 3, lines 4-12 and 20-23, and page 4, lines 10-14. No new matter is being added.

The Applicants reserve the right to prosecute, in this or one or more other patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. For example, the Applicants reserve the right to re-instate, or file a divisional or other patent application claiming, any subject matter no longer explicitly included in the amended claims.

If it would facilitate the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,

Loretta J. Henderson
Attorney for Applicants
Registration No. 37,347

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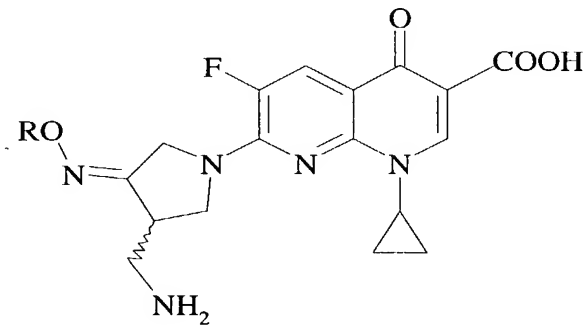
N:\loretta\applications\P32411\prelim.doc

Appendix 1

Marked-up version of claim 1 amendment made March 1, 2002

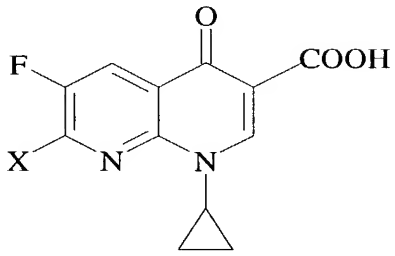
added text shown by underlineation

1. (once amended) A process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:



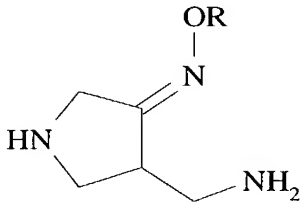
(I)

wherein R is C_{1-4} alkyl or C_{1-4} haloalkyl, which comprises reaction of a compound of formula (II):



(II)

wherein X is a leaving group; with a compound of formula (III):



(III)

wherein R is as defined for formula (I), or a salt thereof;

in the presence of a base and an aqueous solvent, wherein the solvent is water;

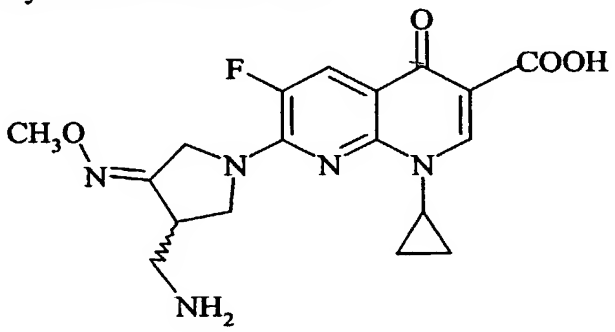
and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

PCT/PTO 01 MAR 2002
10/070281
PCT/GB00/03366

PROCESS FOR PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES

The present invention relates to a novel process for the production of pharmaceutically active compounds, for example, quinolone carboxylic acid derivatives having antibacterial activity.

EP 688772 discloses novel naphthyridine carboxylic acid derivatives having antibacterial activity, including anhydrous (R,S)-7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of the formula:

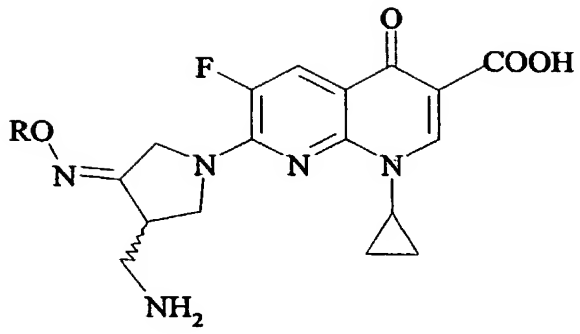


WO 98/42705 discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate.

EP 688772 discloses a process for the production of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid which comprises the reaction of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 4-aminomethyl-3-methoxyiminopyrrolidinium ditrifluoroacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene using dry acetonitrile as solvent. PCT/KR99/00099 (published after the priority date of the present application) discloses the same process using 4-aminomethyl-3-methoxyiminopyrrolidinium dihydrochloride.

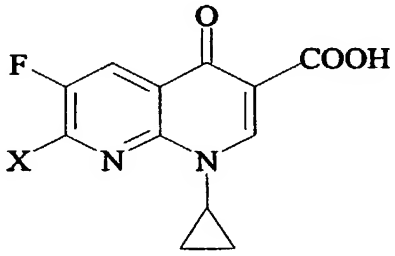
The present invention relates to an improved process for the production of quinoline carboxylic acid derivatives having antibacterial activity.

Thus according to the invention there is provided a process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:



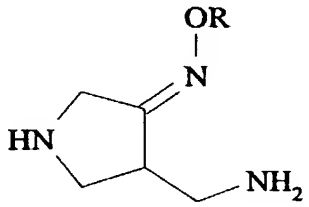
(I)

wherein R is C_{1-4} alkyl or C_{1-4} haloalkyl, which comprises reaction of a compound of formula (II):



(II)

wherein X is a leaving group; with a compound of formula (III):



(III)

wherein R is as defined for formula (I), or a salt thereof; in the presence of a base and an aqueous solvent;

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

Suitable aqueous solvents for use in the process according to the invention include aqueous acetonitrile and aqueous alcohols, e.g. aqueous C_{1-6}alkyl alcohols such as aqueous ethanol; however the preferred solvent is water.

When the solvent used for the process is a mixed solvent any ratio of solvents may be used, for example when the solvent is aqueous acetonitrile a ratio of between 0.7 and 1.4 acetonitrile:water may be used, preferably 1:1 acetonitrile:water.

The reaction is preferably performed in greater than 1 volume of solvent based on the compound of formula (II), for example 10 volumes of solvent.

The reaction is preferably performed using an excess of the compound of formula (III) to the compound of formula (II), for example between 1.01 and 1.08

mole equivalents of the compound of formula (III), preferably 1.05 mole equivalents.

The reaction is preferably performed at a temperature between ambient and 100°C, for example between ambient and about 60°C.

Suitable bases for use in the process of the invention include organic bases such as triethylamine, diisopropylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene and 1,4-diazabicyclo[2.2.2]octane, and tetraalkylammonium hydroxides, e.g. a tetraC_{1-6}alkyl alkylammonium hydroxide such as tetrabutylammonium hydroxide or tetramethylammonium hydroxide. Inorganic bases such as sodium and potassium hydrogen carbonate, sodium and potassium hydroxide and sodium and potassium carbonate may also be used.

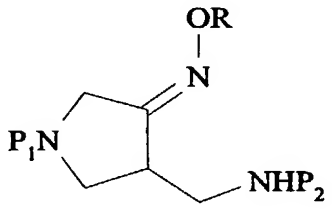
The base is preferably triethylamine.

Suitably between 3.2 and 3.8 mole equivalents of base are used based on the compound of formula (II), preferably 3.4 mole equivalents of base are used. When the base is a tetraalkylammonium hydroxides then the process may use less than 3 equivalents, e.g. about 2.6 equivalents, of the base.

Suitable leaving groups X in the compound of formula (II) include halogens, particularly chloro, other suitable leaving groups will be apparent to those skilled in the art.

The compound of formula (III) is preferably in the form of the dimethanesulfonate salt, e.g. 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate. Other salts of the compound of formula (III) include the hydrochloride, trifluoroacetate and sulfate salts.

Dimethanesulfonate salts of the compound of formula (III) may be produced by a process comprising reaction of a compound of formula (IV):



(IV)

wherein R is as defined for formula (I) and P_1 and P_2, which may be the same or different, are amino protecting groups, with methanesulfonic acid.

Suitable protecting groups P_1 and P_2 include any suitable amino protecting groups which are removable by treatment with methanesulfonic acid. The preferred protecting group for both P_1 and P_2 is t-butoxycarbonyl.

The reaction of the compound of formula (II) and methanesulfonic acid is suitably carried out at a temperature between about 10°C and about 50°C, more preferably at a temperature of 40-45°C.

The amount of methanesulfonic acid used to effect the deprotection of the compound of formula (II) is suitably 2 to 4 equivalents. For example, 2.4 equivalents, suitably used at a temperature of between 35°C and 40°C; or 3

equivalents, suitably used at ambient temperature. More preferably 2.5 equivalents used at a temperature of 40-45°C.

The reaction is suitably carried out in a solvent, for example, an alcohol such as methanol, ethanol, isopropanol, or n-propanol, dichloromethane, acetonitrile, acetone, methyl iso-butyl ketone, DME, THF, tert-butylmethyl ether, dioxane or ethyl acetate or a mixture of any of these. The solvent is preferably methanol. Suitably, up to 10 equivalents by volume of solvent may be used, e.g. about 4 equivalents.

The compounds of formula (II), (III) and (IV) may be prepared by the processes described in US 5,633,262, EP 688772 and PCT/KR99/00099.

The compound of formula (I) produced according to the invention is preferably (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate or a hydrate thereof, preferably the sesquihydrate, as disclosed in WO 98/42705. The methanesulfonate and hydrates thereof may be synthesised from the free acid as described in WO 98/42705 and WO 00/17199.

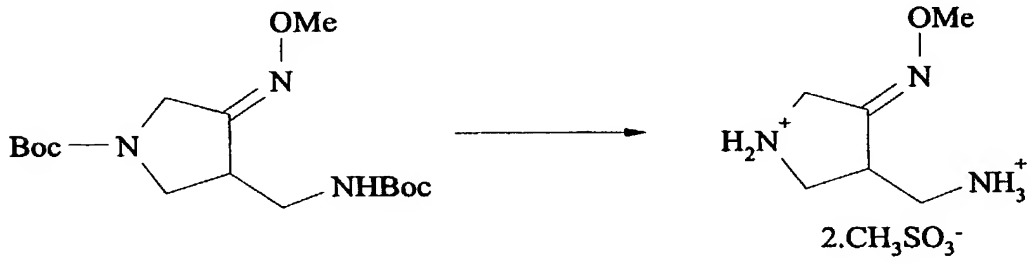
The process of the invention has the advantages that it produces drug substance of superior quality compared to the known process using dry acetonitrile as solvent. In addition the use of an aqueous solvent is more cost effective and may offer environmental advantages.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following examples. However, it should be understood that the examples are intended to illustrate but not in any manner limit the scope of the invention.

Example 1

Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate



A solution of 1-(N-t-butoxycarbonyl)-4-(t-butoxycarbonylaminomethyl) pyrrolidin-3-methoxime (100g) in methanol (660mL) at 15-20°C under nitrogen was treated with methanesulfonic acid (56.4mL) over 5 min keeping the temperature below 30°C. The solution was stirred at 20-25°C for 16-20hrs. During this time the product precipitated forming a thick suspension. The product was isolated by filtration, washed with methanol (165ml) and dried under vacuo at 25°C to give the title compound 84g

(86%).
m.p. 189-193°C;
m/z: 144 $(M+H)^+$;
^{1}H NMR (400MHz, d_6-DMSO) δ: 9.27, (2H, brs), 7.95 (3H, brs), 4.01 (1H, d), 3.92 (1H, d), 3.87 (3H, s), 3.69 (1H, m), 3.26 (2H, m), 3.26 (2H, m), 3.15 (1H, m), 3.08 (1H, m), 2.39 (6H, s);
Analysis: C, 28.64%, H, 6.25%, N, 12.46%; $C_8H_{21}N_3O_7S_2$ requires C, 28.65%, H, 6.31%, N, 12.53%.

Example 2
Synthesis of 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate

A solution of 1-(N-t-butoxycarbonyl)-4-(t-butoxycarbonylaminomethyl) pyrrolidin-3-methoxime (100g) in methanol (400mL) at 20°C under nitrogen was treated with methanesulfonic acid (47mL, 70g, 2.5 equiv) over 15 min keeping the temperature below 25°C. The solution was heated to 40-45°C over 30 mins and maintained at this temperature for 4-5 hrs. During this time the product precipitated forming a thick suspension. The crude product was isolated by filtration under nitrogen and washed with methanol (200mL). The crude product was suspended in methanol (4 volumes, approx. 360mL) and heated to reflux for 1 hr. After cooling to 20°C the suspension was stirred for 1 hour. The product was filtered, washed with methanol (2 volumes, approx. 180ml) and dried under vacuum at 40°C to give the title compound 73.8g (78%).
Characterising data were consistent with a standard sample of the title compound.

Example 3
Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Triethylamine (5.1ml) was added to 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (3.05g) in water (25ml) at 15-20°C and the mixture stirred for 20 min. 4-Aminomethyl-3-methoxyimino-pyrrolidinium dimethanesulfonate (3.86g) was added, followed by water (5ml), and the mixture stirred at 20-25°C for 17¾ hours. The resulting product was filtered and the cake washed with water (30ml) followed by ethanol (30ml) and dried under vacuum at 50°C to give the title compound as a white solid (4.23g). (102% as is, 86% on assay).
Characterising data were consistent with a standard sample of the title compound.

Example 4
Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Triethylamine (34ml) was added to 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (20.17g) in a mixture of acetonitrile (100ml) and water (100ml) at 15-20°C and the mixture stirred for 30 min. 4-Aminomethyl-3-methoxyiminopyrrolidinium dihydrochloride (18.9g) was added, followed by water (5ml), and the mixture stirred at 20-25°C for 23¼ hours. The

resulting product was filtered and the cake washed with ice-cold 1:2 acetonitrile:water (100ml) followed by acetonitrile (100ml), air dried, then dried under vacuum, at ambient temperature, to give the title compound as a fawn solid (26g). (94% as is, 78.8% on assay). Characterising data were consistent with a standard sample of the title compound.

Example 5

Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

A 40% solution of tetrabutylammonium hydroxide in water (15 ml, 23 mmol) was added to a mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (2.5 g, 8.8 mmol) and 4-amino-methyl-3-methoxyiminopyrrolidinium dimethanesulfonate (3.12 g, 9.3 mmol) in water (8 ml) at 20 - 25°C and the mixture stirred for 24 hours. The resulting product was filtered and the cake washed with water (25 ml) followed by ethanol (25 ml) and dried under vacuum at 50°C to give the title compound as a white solid (3.47 g). Characterising data were consistent with a standard sample of the title compound.

Example 6

Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate

A solution of methanesulfonic acid (0.33 g, 3.43 mmol) in dichloromethane (1 ml) was added to a suspension of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (1.5 g at 89.9% purity, 3.46 mmol) in a mixture of dichloromethane (23.2 ml) and ethanol (2.7 ml) at 30°C. The mixture was stirred at 30°C for 3 hours then cooled to 20°C and filtered. The cake was washed with dichloromethane (20 ml) and dried at 50°C under vacuum to give the title compound (1.71 g) (102% as is, 91% on assay). Characterising data were consistent with a standard sample of the title compound.

Example 7

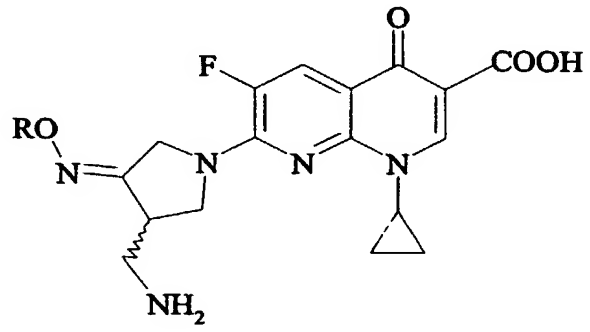
Synthesis of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate

(R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate (27.5 g at 91% purity, 51.4 mmol) was stirred in a mixture of isopropanol (150 ml) and water (75 ml) and heated until a clear solution was obtained (52°C). The solution was cooled to 34°C and seed crystals of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate added. The resulting suspension was allowed to cool to

25°C over 1 hour and stirred for 18 hours. The slurry was cooled to 0 - 4°C, stirred for 2 hours, then filtered and the cake washed with isopropanol (30 ml). The product was sucked dry for 2 hours and then further dried at 50°C under vacuum. The dried product was exposed to the atmosphere to give the sesquihydrate, 22.9 g (92%). Characterising data were consistent with a standard sample of the title compound.

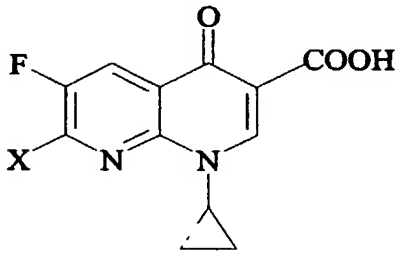
CLAIMS

1. A process for the production of a compound of formula (I), or a pharmaceutically acceptable salt and/or hydrate thereof:



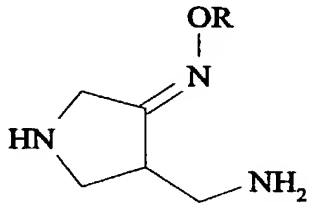
(I)

wherein R is C_{1-4} alkyl or C_{1-4} haloalkyl, which comprises reaction of a compound of formula (II):



(II)

wherein X is a leaving group; with a compound of formula (III):



(III)

wherein R is as defined for formula (I), or a salt thereof; in the presence of a base and an aqueous solvent;

and optionally forming a pharmaceutically acceptable salt and/or hydrate thereof.

2. The process according to claim 1 wherein the solvent is aqueous acetonitrile, an aqueous alcohol or water.

3. The process according to claim 2 wherein the solvent is water.

4. The process according to any one of the preceding claims wherein 10 volumes of solvent based on the compound of formula (II) are used.

5. The process according to any one of the preceding claims wherein between 1.01 and 1.08 mole equivalents of the compound of formula (III) based on the compound of formula (II) are used.

6. The process according to any one of the preceding claims performed at a temperature between ambient and about 60°C.

7. The process according to any one of the preceding claims wherein the base is triethylamine.

8. The process according to any one of the preceding claims wherein between 3.2 and 3.8 mole equivalents of base is used based on the compound of formula (II).

9. The process according to any one of the preceding claims wherein X is chloro.

10. The process according to any one of the preceding claims wherein the compound of formula (III) is 4-aminomethyl-3-methoxyiminopyrrolidinium dimethanesulfonate.

11. The process according to any one of the preceding claims wherein the compound of formula (I) is (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate.

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Published:
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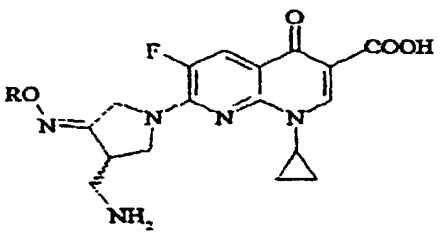
(54) Title: PROCESS FOR PRODUCTION OF NAPHTHYRIDINE-3-CARBOXYLIC ACID DERIVATIVES

(57) Abstract: A process for the production of Naphthyridine-3-carboxylic acid derivatives of formula (I) having antibacterial activity.



(I)

WO 01/18002 A1

Docket No.: P32411 PCT/GB00/03366

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Process for production of naphthyridine-3-carboxylic acid derivatives

the specification of which (check one)
[ ] is attached hereto.
[X] was filed on 01 September 2000 as Serial No. PCT/GB00/03366
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9920917.3	Great Britain	03 September 1999	Yes

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

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Serial No.	Filing Date	Status

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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